A clean copy of the entire set of pending claims is set forth in Appendix A.

IN THE SPECIFICATION:

Please add the related application information, as indicated in Appendix D. A clean copy of the related application information is set forth in Appendix C.

IN THE DRAWINGS:

F10 Please delete Figures 7A-7F and replace with Figures 7A-7F submitted herewith as Appendix E.

Remarks

Claims 84, 89, 91, 92, 94, 95, 97, 99, 101 and 103 are pending in the application. Claim 97 has been cancelled. Claims 84, 91-92, 94-95, 99, 101 and 103 have been amended. No new matter has been added by way of this amendment. Claims 84, 91, 92, 99, and 103 have been amended to change dependency based on new and elected claims.

New claims 104-120 have been added. No new matter has been added by way of this addition. Support for new claims 104-105 can be found, *e.g.*, at page 25, lines 26-28. Support for new claims 106-108 can be found, *e g.*, at page 25, lines 26-30; and page 26, line 4. Support for new claim 109 can be found, *e.g.*, at page 28, lines 27-35. Support for new claim 110 can be found, *e.g.*, at page 29, lines 14-28. Support for new claim 111 can be found, *e g.*, at page 25, lines 2-5. Support for new claim 112 can be found, *e.g.*, at page 21, lines 10-17. Support for new claim 113 can be found, *e.g.*, at page 21, line 18-page 22, line 1. Support for new claims 114-115 can be found, *e.g.*, at page 12, lines 2-5, and page 39, lines 16-18. New claim 116

essentially corresponds to cancelled claim 97. Support for new claim 117 and amended claims 94 and 95 can be found throughout the specification, *e.g.*, at page 12, lines 10-13; and page 38, lines 19-22. Support for new claims 118-119 can be found, *e.g.*, at page 36, lines 20-24. Support for new claim 120 can be found, *e.g.*, at page 25, lines 19-25; and page 33, line 29-page 35, line 8.

A marked up copy of both the new and amended claims is set forth in Appendix B. A clean copy of the entire set of pending claims is set forth in Appendix A for the Examiner's convenience.

The specification has been amended to update the related application information (Appendices C-D). Additionally, Figures 7A-7F have been replaced to correct the margins (Appendix E), as indicated on Form 948 (dated 28 June 2002). No new matter has been added by way of these amendments.

Thus, after entry of this amendment, claims 84, 89, 91-92, 94-95, 101, and 103-120 will be pending in this application. Applicants respectfully request reconsideration of pending claims 84, 89, 91-92, 94-95, 101 and 103-120.

I. Rejection Under 35 U.S.C. § 112, Second Paragraph.

Several claims were rejected under 35 U.S.C. § 112, second paragraph as being indefinite. For completeness, each of the several grounds of rejection will be addressed individually.

A. Rejection of Claims 84, 89, 91-92, 94-95, 101.

Claims 84, 89, 91-92, 94-95, 101 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for recitation of "dendritic cell precursors" that "process and present said antigen."

Solely in an effort to advance prosecution of this application, Applicants have amended independent claim 101 (from which all other rejected claims depend) to recite a composition comprising antigen-activated dendritic cells, wherein said antigen-activated dendritic cells are produced from proliferating cell cultures by a given method, and wherein the dendritic cell precursors are cultured in the presence of antigen for a time sufficient to allow antigen processing and presentation to occur.

No new matter has been added by way of this amendment, as support can be found in the specification, *e.g.,* at page 20, line 33-page 21, line 17; page 25, lines 19-23; page 28, lines 15-16; page 28, lines 27-30; page 33, line 29-page 35, line 8.

Applicants respectfully submit that independent claim 101, as amended, satisfies the requirements of 35 C.F.R. § 112, second paragraph. Likewise, claims 84, 89, 91-92, and 94-95 (as well as dependent claim 103 and new claims 104-119), which are either directly or indirectly dependent on claim 101, as amended, and thus contain all the limitations thereof, also satisfy the requirements of 35 C.F.R. § 112, second paragraph. Accordingly, Applicants respectfully request that this ground of rejection be reconsidered and withdrawn.

B. Rejection of Claims 84, 89, 91-92, 94-95, and 101

Claims 84, 89, 91-92, 94-95, and 101 were rejected under 35 U.S.C. 112, second paragraph for recitation of "antigen-activated" "dendritic cell precursors" (Office Action, page 4).

As described in the previous section, independent claim 101 (from which all other rejected claims depend) has been amended herein to recite to recite a composition comprising antigen-activated dendritic cells, wherein said antigen-activated dendritic cells are produced from proliferating cell cultures by a given method, and wherein the dendritic cell precursors are cultured in the presence of antigen for a time sufficient to allow antigen processing and presentation to occur.

Applicants respectfully submit that independent claim 101, as amended, satisfies the requirements of 35 C.F.R. § 112, second paragraph. Likewise, claims 89, 91-92, 94-95, 101 (as well as dependent claim 103 and new claims 104-119), which are either directly or indirectly dependent on claim 101, as amended, and thus contain all the limitations thereof, also satisfy the requirements of 35 C.F.R. § 112, second paragraph. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

C. Rejection of Claims 91 and 92.

Claims 91 and 92 were rejected under 35 U.S.C. § 112, second paragraph, for depending on cancelled claim 83.

Applicants have amended claims 91 and 92 herein to depend on pending claim 89.

D. Rejection of Claims 97, 99, and 103.

Claims 97, 99, and 103 were rejected under 35 U.S.C. § 112, second paragraph, for depending on non-elected claim 96.

Applicants have cancelled claim 97 and amended claims 99 and 103 to depend on new claim 116.

E. Rejection of Claim 95.

Claim 95 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "vague and indefinite" for the recitation of "the mycotuberculosis bacteria is BCG."

Claim 94 (from which claim 95 depends) has been amended to recite that the antigen is a mycobacteria. Claim 95 has been amended to recite that the mycobacteria is BCG. Applicants have also added new claim 117, which recites that the mycobacteria is a tuberculosis bacteria.

Applicants respectfully submit that amended claims 94 and 95, and new claim 117, satisfy all the requirements of 35 C.F.R. § 112, second paragraph. Accordingly, Applicants respectfully request that these rejections be reconsidered and withdrawn.

II. Rejection Under 35 U.S.C. § 112, First Paragraph.

Claim 99 was rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly lacks written description of the claimed invention.

Applicants respectfully traverse this ground of rejection.

The Examiner opines that this "is a new matter rejection" and that "the specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the recitation of 'wherein the antigen-activated dendritic cells express an amount of modified antigen to provide between about 1 to 100 micrograms of modified antigen in said pharmaceutical composition'" (Office Action, page 5).

In response, Applicants respectfully direct the Examiner's attention to the paragraph spanning lines 9-24 on page 42, and specifically lines 22-25 for support.

Applicants respectfully submit that claim 99 satisfies all the requirements of 35 C.F.R. § 112, first paragraph. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

III. Rejection Under 35 U.S.C. § 103(a).

Claims 89, 91-92, 94-95, 97, 99, 101, and 103 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Inaba *et al.* (1990), in view of Aldovini *et al.* (1991).

As described in detail elsewhere herein, Applicants have amended independent claim 101 (from which all other rejected claims depend) to recite a composition comprising antigen-activated dendritic cells, wherein said antigen-activated dendritic cells are produced from proliferating cell cultures by a given method, and wherein the dendritic cell precursors are cultured in the presence of antigen for a time sufficient to allow antigen processing and presentation to occur.

Inaba *et al.* was cited to teach dendritic cells pulsed with polypeptide or peptide antigens that process and present antigen. Inaba *et al.* teaches that mouse T cells can be primed *in situ*

using fresh, splenic dendritic cells pulsed with protein antigen. However, Inaba *et al.* does not teach a composition of antigen-activated dendritic cells produced by the method recited in independent claim 101. Inaba *et al.* also does not teach a composition of antigen-activated dendritic cells derived from a population of proliferating precursor cells contacted *in vitro* with antigen in the presence of GM-CSF, as recited in new independent claim 120.

To supply the deficiency in Inaba *et al.,* the Examiner cites Aldovini *et al.* However, Aldovini *et al.* simply teaches the BCG antigen, and does nothing to supply the deficiency of Inaba *et al.* Moreover, Aldovini *et al.*, either alone or in combination with Inaba *et al.,* does not teach or suggest a composition of antigen-activated dendritic cells produced by the method recited in independent claim 101, nor the composition of antigen-activated dendritic cells, as recited in new independent claim 120.

Furthermore, even *if* the combination of Inaba *et al.* and Aldovini *et al.* did teach or suggest a composition of antigen-activated dendritic cells produced by the method recited in independent claim 101 (or the composition of antigen-activated dendritic cells, as recited in new independent claim 120), Applicants respectfully submit that there was no motivation to combine these references. "To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); *see also In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art

references."); *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (modification of the teachings of a prior art reference is not established by the teachings of a second prior art reference "*unless the prior art suggests the desirability of the modification*" (emphasis added)). Thus, Applicants respectfully submit that the motivation to combine the cited references is completely lacking.

Applicants respectfully submit that independent claim 101, as amended, is non-obvious in view of the teachings of Inaba *et al.* and Aldovini *et al.* Similarly, claims 89, 91-92, 94-95, 97, 99, 101, and 103 (as well as claim 84 and new claims 104-119), wherein they depend directly or indirectly upon independent claim 101, as amended, and thus contain all the limitations thereof, also satisfy the requirements of 35 U.S.C. § 103(a).

Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

Claim 84 was also rejected under 35 U.S.C. § 103(a) as being unpatentable over Inaba *et al.* (1990) in view of Aldovini *et al.* (1991), as applied above, and in further view of Caux *et al.* (199) as evidenced by Romani *et al.* (1994).

The Inaba *et al.* and Aldovini *et al.* references are discussed above.

To supplement the deficiencies of Inaba *et al.* and Aldovini *et al.*, the Examiner cites Caux *et al.*, which is cited to teach human dendritic cell precursors cultured with GM-CSF and TNFα.

However, Caux *et al.* does not teach a composition of antigen-activated dendritic cells produced by the method recited in amended independent claim 101 (from which claim 84

depends). Thus, Applicants respectfully submit that Caux *et al.* does nothing to supplement the deficiencies in the teachings of Inaba *et al.* and Aldovini *et al.*, and, thus, the combination does not render independent claim 101, as amended herein, obvious over the cited art. Furthermore, Applicants respectfully submit that the motivation to combine the Inaba *et al.*, Aldovini *et al.*, and Caux *et al.* references is completely lacking.

With respect to the Romani *et al.* reference, Applicants respectfully point out that this reference was published in 1994, which is 2 years after the earliest claimed priority date of the instant application (1992). Thus, Applicants respectfully submit that citation of the Romani *et al.* reference in this ground of rejection is inappropriate.

Thus, Applicants respectfully submit that independent claim 101, as amended, satisfies all the requirements of 35 C.F.R. § 103(a). Likewise claim 84, wherein it depends directly upon independent claim 101, as amended, and thus contains all the limitations thereof, also satisfies the requirements of 35 U.S.C. § 103(a).

Accordingly, Applicants respectfully request that this ground of rejection be reconsidered and withdrawn.

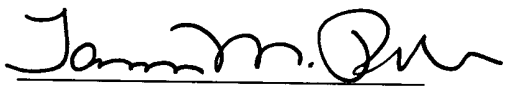
IV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

A Petition for a two month Extension of Time under 37 C.F.R. § 1.136(a) is filed concurrently herewith, which extends the response period from 02 October 2002 to 02 December 2002. The Petition further authorizes the PTO to charge the two month extension fee of $200 to our Deposit Account No. 08-0219, which reflects Applicants' Small Entity Status.

If there are any other fees due in connection with the filing of the response, please charge the fees to our Deposit Account No. 08-0219. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above or in the Petition filed concurrently herewith, such an extension is requested and the fee should be charged to our Deposit Account. Also, please charge any fees underpaid or credit any fees overpaid to the same Deposit Account.

Respectfully submitted,



Tamera M. Pertmer, Ph.D.
Agent for Applicant
Registration No. 47,856

Date: 12/02/02

HALE AND DORR LLP
60 State Street
Boston, MA 02109
Tel: (617) 526-6000
Fax: (617) 526-5000

APPENDIX A

Pending Claims 84, 89, 91-92, 94-95, 99, 101, and 103-120

F1 84. (Three Times Amended) The composition according to claim 101, wherein the dendritic cell precursors are human.

F2 89. The composition according to claim 101, wherein the antigen is a microorganism.

F3 91. (Amended) The composition according to claim 89 wherein the antigen is a polypeptide.

92. (Amended) The composition according to claim 89 wherein the antigen is a peptide.

F4 94. (Three Times Amended) The composition according to claim 101, wherein the antigen is a mycobacteria.

F5 95. (Twice Amended) The composition according to claim 94, wherein the mycobacteria is BCG.

F6 99. (Twice Amended) The pharmaceutical composition according to claim 116, wherein the antigen-activated dendritic cells express an amount of antigen to provide between about 1 to 100 micrograms of antigen in said pharmaceutical composition.

F7 101. (Three Times Amended) A composition comprising antigen-activated dendritic cells, wherein said antigen-activated dendritic cells are produced from proliferating cell cultures by a method comprising:

providing a tissue source comprising dendritic cell precursors;

optionally treating the tissue source comprising dendritic cell precursors to increase the proportion of dendritic cell precursors;

culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain cell clusters;

subculturing the cell clusters to produce cell aggregates comprising proliferating dendritic cell precursors; and

subculturing the cell aggregates at least one time to enrich the proportion of dendritic cell precursors;

wherein the dendritic cell precursors are cultured in the presence of antigen for a time sufficient to allow antigen processing and presentation to occur.

103. (Amended) The pharmaceutical composition according to claim 116, wherein the pharmaceutical composition comprises from about $1x10^6$ to $1x10^7$ antigen-activated dendritic cells.

104. (New) The composition according to claim 101, wherein the tissue source is blood.

105. (New) The composition according to claim 101, wherein the tissue source is bone marrow.

106. (New) The composition according to claim 101, wherein GM-CSF is present in the culture medium at a concentration of about 1-1000 U/ml.

107. (New) The composition according to claim 104, wherein the concentration of GM-CSF in the culture medium is about 30-100 U/ml.

108. (New) The composition according to claim 105, wherein the concentration of GM-CSF in the culture medium is about 500-1000 U/ml.

109. (New) The composition according to claim 101, wherein the cell aggregates are subcultured from about one to five times.

110. (New) The composition according to claim 101, wherein the cell aggregates are subcultured about every 3 to 30 days.

111. (New) The composition according to claim 101, wherein the culture medium is selected from the group consisting of RPMI 1640, DMEM, and α-MEM, and wherein the culture medium is supplemented with serum.

112. (New) The composition according to claim 104, wherein the tissue source is treated to remove red blood cells.

113. (New) The composition according to claim 105, wherein the tissue source is treated to remove B cells and granulocytes.

114. (New) The composition according to claim 101, wherein said antigen is presented by the dendritic cells on MHC class I or MHC class II.

115. (New) The composition according to claim 101, wherein said modified antigen is presented by the dendritic cells on MHC class I and MHC class II.

116. (New) A pharmaceutical composition comprising a therapeutically effective amount of the composition according to claim 101.

117. (New) The composition according to claim 94, wherein the mycobacteria is a tuberculosis bacteria.

118. (New) The composition according to claim 101, wherein the dendritic cell precursors are cultured in the presence of antigen for between about 1-48 hours.

119. (New) The composition according to claim 118, wherein the dendritic cell precursors are cultured in the presence of antigen for about 20 hours.

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120. (New) A composition comprising antigen-activated dendritic cells, wherein said antigen-activated dendritic cells are derived from a population of proliferating precursor cells which were contacted *in vitro* with antigen in the presence of GM-CSF for a sufficient time for antigen processing and presentation to occur.

APPENDIX B

Amended Claims 84, 91-92, 94-95, 99, 101, 103 and New Claims 104-120

Please cancel claim 97.

Please amend claims 84, 91-92, 94-95, 99, 101, and 103 as follows:

84. (Three Times Amended) The composition [of dendritic cell precursors] according to [either one of claims 82 or] claim 101, wherein the dendritic cell precursors are human.

91. (Amended) The composition according to claim [83] 89 wherein the antigen is a polypeptide.

92. (Amended) The composition according to claim [83] 89 wherein the antigen is a peptide.

94. (Three Times Amended) The composition according to claim 101, wherein the antigen is a mycobacteria [tuberculosis bacteria].

95. (Twice Amended) The composition according to claim 94, wherein the mycobacteria [tuberculosis bacteria] is BCG.

99. (Twice Amended) The pharmaceutical composition according to claim [97] 116, wherein the antigen-activated dendritic cells express an amount of [modified] antigen to provide between about 1 to 100 micrograms of [modified] antigen in said pharmaceutical composition.

101. (Three Times Amended) [An *in vitro*] A composition comprising [a population of] antigen-activated dendritic [cell precursors] cells, wherein said antigen-activated dendritic [cell precursors present processed antigen derived from an enriched and expanded population of

proliferating dendritic cell precursors, which were contacted *in vitro,* in the presence of GM-CSF, with antigen for sufficient time for said proliferating dendritic cell precursors to process and present said antigen] cells are produced from proliferating cell cultures by a method comprising:

providing a tissue source comprising dendritic cell precursors;

optionally treating the tissue source comprising dendritic cell precursors to increase the proportion of dendritic cell precursors;

culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain cell clusters;

subculturing the cell clusters to produce cell aggregates comprising proliferating dendritic cell precursors; and

subculturing the cell aggregates at least one time to enrich the proportion of dendritic cell precursors;

wherein the dendritic cell precursors are cultured in the presence of antigen for a time sufficient to allow antigen processing and presentation to occur.

103. (Amended) The pharmaceutical composition according to claim [97] 116, wherein the pharmaceutical composition comprises from about $1x10^6$ to $1x10^7$ antigen-activated dendritic [cell precursors] cells.

Please add new claims 104-120 as follows:

--104. (New) The composition according to claim 101, wherein the tissue source is blood.

105. (New) The composition according to claim 101, wherein the tissue source is bone marrow.

106. (New) The composition according to claim 101, wherein GM-CSF is present in the culture medium at a concentration of about 1-1000 U/ml.

107. (New) The composition according to claim 104, wherein the concentration of GM-CSF in the culture medium is about 30-100 U/ml.

108. (New) The composition according to claim 105, wherein the concentration of GM-CSF in the culture medium is about 500-1000 U/ml.

109. (New) The composition according to claim 101, wherein the cell aggregates are subcultured from about one to five times.

110. (New) The composition according to claim 101, wherein the cell aggregates are subcultured about every 3 to 30 days.

111. (New) The composition according to claim 101, wherein the culture medium is selected from the group consisting of RPMI 1640, DMEM, and α-MEM, and wherein the culture medium is supplemented with serum.

112. (New) The composition according to claim 104, wherein the tissue source is treated to remove red blood cells.

113. (New) The composition according to claim 105, wherein the tissue source is treated to remove B cells and granulocytes.

114. (New) The composition according to claim 101, wherein said antigen is presented by the dendritic cells on MHC class I or MHC class II.

115. (New) The composition according to claim 101, wherein said antigen is presented by the dendritic cells on MHC class I and MHC class II.

116. (New) A pharmaceutical composition comprising a therapeutically effective amount of the composition according to claim 101.

117. (New) The composition according to claim 94, wherein the mycobacteria is a tuberculosis bacteria.

118. (New) The composition according to claim 101, wherein the dendritic cell precursors are cultured in the presence of antigen for between about 1-48 hours.

119. (New) The composition according to claim 118, wherein the dendritic cell precursors are cultured in the presence of antigen for about 20 hours.

120. (New) A composition comprising antigen-activated dendritic cells, wherein said antigen-activated dendritic cells are derived from a population of proliferating precursor cells which were contacted *in vitro* with antigen in the presence of GM-CSF for a sufficient time for antigen processing and presentation to occur.--

APPENDIX C

AMENDMENT TO SPECIFICATION (CLEAN VERSION)

This application is a divisional of U.S. Serial No. 08/458,230, filed June 2, 1998 (now U.S. Patent No. 5,851,756), which is a continuation of U.S. Serial No. 08/040,677, filed March 31, 1993 (abandoned), which is a continuation-in-part of U.S. Serial No. 07/981,357, filed November 25, 1992 (abandoned), which is a continuation-in-part of U.S. Serial No. 07/861,612, filed April 1, 1992 (abandoned).

APPENDIX D

AMENDMENT TO SPECIFICATION (MARKED-UP VERSION)

On page 1, after the title, please insert the related application information as follows:

--This application is a divisional of U.S. Serial No. 08/458,230, filed June 2, 1998 (now U.S. Patent No. 5,851,756), which is a continuation of U.S. Serial No. 08/040,677, filed March 31, 1993 (abandoned), which is a continuation-in-part of U.S. Serial No. 07/981,357, filed November 25, 1992 (abandoned), which is a continuation-in-part of U.S. Serial No. 07/861,612, filed April 1, 1992 (abandoned).--

APPENDIX E

REPLACEMENT FIGURES 7A-7F